**Interaction between CNS-resident cells and gut dysbiosis in multiple sclerosis**

**Consequences on neuroinflammation**

Garcia García, Joana. Degree in Biomedical Sciences, Universitat Autònoma de Barcelona

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**Introduction**

Neuroinflammation is a hallmark of multiple sclerosis (MS), in which microglia and astrocytes are key players. Given the multifactorial etiology, gut dysbiosis has emerged as a potential pathogenic factor. Despite being extensively studied how microbial immunomodulatory metabolites impact on T lymphocytes, less is known about the effects on microglial and astrocytic activity and the consequences on neuroinflammation.

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**Aims**

- To describe the profile of gut microbiota in patients with MS.
- To determine the role of CNS-intrinsic cells (microglia and astrocytes) in MS pathogenesis.
- To analyse the interaction between microbiome and CNS-resident cells, emphasizing in dietary tryptophan metabolites and short-fatty acid chains.
- To study its consequences in regards to the neuroinflammation present in MS.

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**Methodology**

- Search on Pubmed database.
- Selection criteria: Journal impact factor, date of publication (last 5 years) and relation with the review topic.
- Reading and summary of the selected articles, exhaustive analysis of their bibliography.

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**Gut dysbiosis in MS patients**

Gut dysbiosis in MS patients has been constantly observed in several studies, with subtle changes in the relative abundance of some specific bacterial genera. A generalized “MS microbiota phenotype” has not been described, suggesting that many factors can influence its composition (e.g. age, diet, geographical features).

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**Microglia and astrocytes in the pathogenesis of MS**

Whereas in the disease onset neuroprotective M2 microglia and A2 astrocytes promote acral regeneration and remyelination, their neurototic and demyelinating properties predominant to the extent that the disease progresses due to a shift to proinflammatory M1 microglia and reactive A1 astrocytes.

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**Dietary tryptophan metabolites**

Dietary tryptophan metabolites (indoles and other derivatives) act as aryl hydrocarbon receptor (AHR) ligands. In MS patients, circulating levels of AHR agonists are lower in comparison with control individuals. As a consequence, their capability to reduce the proinflammatory phenotype of microglia and astrocytes is impaired and neuroinflammation and MS are worsened.

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**Short-chain fatty acids**

Short-chain fatty acids (SCFAs) are immunomodulatory metabolites. In MS patients, circulating levels of SCFAs are decreased as a consequence of the dysbiosis. SCFAs are important in the modulation of microbial maturation and function; however, little is known about the consequences on neuroinflammation in MS.

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**Conclusions**

- Gut dysbiosis may predominate or modify the course of MS.
- The functional relevance of the interaction between CNS-resident cells and microbiome in MS pathogenesis remains unknown.
- Given the pathogenic role of microglia and astrocytes, determining the specific mechanisms by which gut microbiota, astrocytes and microglia interact may be relevant to develop new therapeutic approaches.
- Most studies have used EAE model or RRMS patients. Studies of gut microbiota in patients with progressive MS may reveal possible other changes in microbial populations.
- It can be extrapolated to other neurodegenerative disease where a dysbiosis has been identified (e.g. Parkinson or Alzheimer diseases).

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**Modulation of neuroinflammation by microbiome in MS**

Dietary tryptophan metabolism leads to two tryptophan metabolites levels, promoting the expression of proinflammatory cytokines, chemokines and neurotoxic factors from astrocytes and microglia directly and also indirectly, through the modulation of the ratio VEGF/VEGFR in microglia. TGFB Thrombosing growth factor alpha, VEGFB Vascular endothelial growth factor B, FBT: Free related tryptase kinase 1, NF-kB: Nuclear factor kappa B, CRP: C-reactive element.

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**References**